REMARKS

This responds to the Office Action mailed on August 8, 2006, and the references cited therewith.

Claims 1-5, 7, 9-18 and 20-23 are now pending in this application.

Claims 1, 2, 7 and 17 have been amended to specify that the label is covalently attached to the external surface of the microsphere. Support of this subject matter can be found throughout the specification and claims as originally filed, for example, in Figure 1 and the Examples (see, e.g. page 34, last paragraph).

Applicant submits that no new matter has been added to the specification or claims.

Election/Restriction

The Examiner has withdrawn claim 23 from prosecution because claim 23 is drawn to proteinoid microspheres made from a subset of amino acids and the label is allegedly not covalently linked to the microsphere.

Claim 23 is directed to a proteinoid microsphere made from particular amino acids (i.e., a mixture of aspartic acid, glutamic acid, asparagine, arginine, and serine amino acids) and linked to a label. Applicant submits that the subject matter of claim 23 is properly part of the present invention because, for example, claim 1 is generic to claim 23. Therefore, Applicant requests reconsideration of the Examiner's restriction. If this request is denied, Applicant requests rejoinder of claim 23 upon allowance of a generic claim.

§103 Rejections of the Claims

To establish a *prima facie* case of obviousness under 35 U.S.C. §103(a), three basic criteria must be met. First, there must be some suggestion or motivation to modify the reference or to combine reference teachings. Second, the reference(s) must teach or suggest all the claim elements. Finally, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed modification and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. See MPEP § 2143.

Claim 1 is drawn to a labeled proteinoid microsphere comprising a mixture of amino acids that are thermally condensed and a label comprising a fluorophore, a chemiluminescent molecule, a radioisotope, a paramagnetic ion, or an enzyme; wherein the label is covalently linked to the external surface of the proteinoid microsphere; and the proteinoid microsphere is stable in solution.

Lohrmann, Steiner and Kayyem

Claims 1, 2, 5, 7, 9, 12-18, 20-22 have been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Lohrmann et al. (U.S. Patent 6,193,953) in view of Steiner et al. (U.S. Patent 4,925,673) and Kayyem et al. (U.S. Patent 6, 232, 295).

Applicant submits that the combination of Lohrmann, Steiner and Kayyem fails to disclose the following elements of the present invention: proteinoid microspheres with labels covalently attached to the external surface of the microspheres. Please note that the present proteinoid microspheres have particular utility for invention signal amplification and/or diagnostic imaging.

Of the three references cited, Steiner is the only reference that mentions proteinoid microspheres. However, Steiner is limited to *encapsulated pharmacological agents* and teaches away from externally attaching agents to the surface of the microspheres. For example, in Example 4 shows that external attachment of insulin to microspheres was an ineffective delivery vehicle. Thus, after consulting Steiner, one of skill in the art would be discouraged from externally attaching agents to the surface of a microsphere.

The Lohrmann disclosure is limited to ultrasound contrast microparticles made of a protein shell and encapsulated air or gas. As the Examiner has stated, Lohrmann does not disclose proteinoid microspheres. Applicant submits that Lohrmann would not guide one skill in the art to external labeling of proteinoid microspheres because air is not readily covalently attached to the external surface of either a proteinoid microsphere or the protein ultrasound microspheres of Lohrmann, and Lohrmann does not teach attachment of other labels to the external surface of the microspheres. Moreover, if one of skill in the art were to try to combine Steiner with Lohrmann, the teachings of Steiner would discourage that skilled artisan from doing

so by teaching that agents should not be attached to the surface of the microspheres and by disclosing the following:

> [P]roteinoids are far more resistant than proteins to cleavage by digestive enzymes. Steiner, col. 3, lines 27-29.

Thus, one of skill in the art would conclude from the teachings of Steiner that proteins are more labile than proteinoid microspheres, and one of skill in the art would not turn to the teachings on proteins by Lohrmann or Kayyem for information on making and using proteinoid microspheres.

In addition, neither Steiner nor Lohrmann disclose the labels contemplated by the present invention. In particular, the terms "fluorophore," "chemiluminescent," "radioisotope," and "paramagnetic" appear nowhere in either of the Steiner or Lohrmann disclosures. The term "enzyme" appears in the Steiner disclosure but only in the context of digestive enzymes that may be present in the person to whom the encapsulated pharmacological agents may be administered. Thus, the teachings of Lohrmann are irrelevant and one of skill in the art would not be tempted to use the microspheres of Steiner to covalently attach any of the present labels to the external surface of a microsphere. Thus, neither Steiner nor Lohrmann disclose anything about the present invention, which relates to signal amplification and/or diagnostic imaging.

Kayyem fails to describe any microsphere whatsoever. In particular, as shown by Figure 1 of the Kayyem disclosure, which is copied below, Kayyem is limited to polymeric molecules (elements 2 and 3) with contrast agents (5) attached.

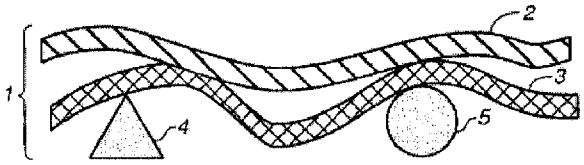

FIG._1A

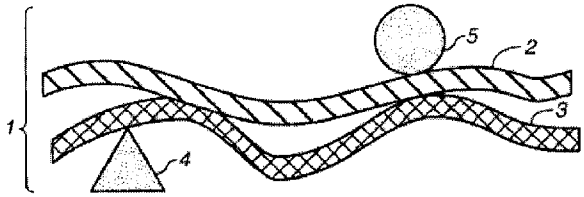

FIG._1B

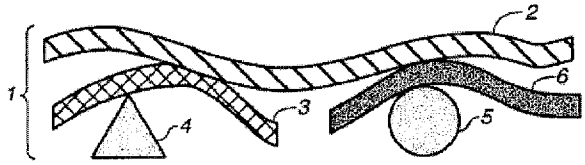

FIG._1C

The polymeric molecules contemplated by Kayyem include proteins (e.g. polylysine) and nucleic acids.

As described above, Steiner would discourage that skilled artisan from using proteins rather than proteinoid microspheres because Steiner teaches that proteinoids are far more resistant than proteins to cleavage by digestive enzymes (col. 3, lines 27-29). Thus, Steiner teaches away from the very thing that Kayyem discloses – use of labile proteins. Accordingly, one of skill in the art would not be motivated to combine the teachings of Steiner and Kayyem.

Moreover, the terms "microsphere" and "microcapsule" appear nowhere in the Kayyem disclosure, thereby further indicating that the teachings of Kayyem are not relevant to those of Steiner and/or Lohrmann. The only "microsphere-like" agent disclosed by Kayyem is a liposome (col. 2, lines 20-32), which Kayyem states is not an ideal contrast agent because liposomal contrast agents suffer from leakiness or long-term retention of the contrast agents in the liver and spleen. Thus, one of skill in the art would not be motivated to combine the polymers of Kayyem with the microspheres of Steiner or Lohrmann because Kayyem teaches away from use of microsphere-like delivery systems such as liposomes.

Nor would one of skill in the art have a reasonable expectation of successfully producing Applicant's invention because Steiner teaches away from using proteins and external attachment of agents while Kayyem teaches away from use of microsphere-like delivery systems. Clearly, the teachings of Kayyem and those of Steiner/Lohrmann are inapposite.

Applicant submits that the combination of Lohrmann (U.S. Patent 6,193,953), Steiner (U.S. Patent No. 4,925,673) and Kayyem et al. (U.S. Patent 6, 232, 295) does not produce the claimed invention and requests withdrawal of this rejection under 35 USC § 103(a).

Lohrmann, Steiner, Kayyem and Mathiowitz

Claims 3, 4, 10 and 11 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Lohrmann et al. (U.S. 6,193,953) in view of Steiner et al. (U.S. Patent 4,925,673), and Kayyem et al. (U.S. Patent 6, 232, 295), and further in view of Mathiowitz et al. (U.S. Patent 5,271,961).

According to the Examiner, Lohrmann et al., Steiner et al. and Kayyem differ from the instant invention in failing to teach that the proteinoid microsphere is formed by thermal condensation of amino acids in the presence of a cross linking agent. However, the Examiner asserts that Mathiowitz discloses that protein microspheres can be modified by cross-linking agents such as glutaraldehyde.

Applicant submits that Mathiowitz fails to cure the defects of Lohrmann, Steiner and Kayyem and provides no motivation to modify the teachings of any of these references to generate the present invention.

Mathiowitz (U.S. Patent No. 5,271,961) is limited to disclosure of methods for incorporating agents into the interior of protein (not proteinoid) microspheres by solvent evaporation of a solution of the agent to be incorporated with proteins (not amino acids).

Applicant submits that, in view of the teachings by Steiner that proteins are more vulnerable to cleavage, one of skill in the art would not turn Mathiowitz teachings on proteins to form microspheres. Instead, one of skill in the art would be discouraged from using the protein microspheres and from using externally labeled microspheres by the teachings of Steiner.

Moreover, Mathiowitz teaches the benefits of using protein microspheres that require only mild conditions for their formation, thereby avoiding thermal degradation of the protein and the encapsulated drug (see, e.g., col. 1, lines 23-32). Thus, upon review of Mathiowitz, one of

skill in the art would be discouraged from using the thermal condensation methods of Steiner to generate microspheres. Not only does Steiner teach away from use of the proteins recited by Mathiowitz, but Mathiowitz teaches away from using the harsh thermal condensation methods of Steiner. Clearly, these references have disparate teachings that would not guide one of skill in the art to the present invention.

For example, if one of skill in the art were to use the amino acids of Steiner with the crosslinkers of Mathiowitz, that artisan would first attach the crosslinker to the Steiner amino acids (see Mathiowitz at col. 6, lines 58-62) and then evaporate the solvent from the amino acids under gentle conditions as specified by Mathiowitz (see, e.g., col. 6, lines 55-58). Applicants submit that such a procedure would yield a mixture of amino acids, some of which would have a crosslinker attached, rather than a microsphere because thermal condensation is needed to make proteinoid microspheres.

Thus, mere mention of a cross-linker in a reference does not mean that one of skill in the art would necessarily know how or why to use the cross-linking agent. There must be some teaching in the cited references to motivate one of skill in the art to make and use the invention as claimed. Here, there is none because Mathiowitz contemplates making protein microspheres for controlled or target drug delivery (col. 2, lines 10-16) under gentle conditions and does not disclose any reason to stabilize those protein microspheres by crosslinking.

Moreover, Mathiowitz is limited to incorporation of agents into microspheres rather than covalently attaching agents to the external surface of the microsphere. Thus, Mathiowitz teaches throughout the specification that agents are incorporated into the microspheres rather than displayed on the exterior of microspheres. For example, Mathiowitz specifically states that, "Compounds are readily incorporated into the microspheres for subsequent release" (col. 2, lines 43-44; see also, Abstract; col. 7, line 64 to col. 8, line 51). Therefore, one of skill in the art would not turn to Mathiowitz to generate a proteinoid microsphere made by thermal condensation of amino acids, where the microsphere has a label covalently attached to the external surface of the microsphere.

Neither Lohrmann nor Kayyem cures this defect because nowhere does Lohrmann or Kayyem disclose proteinoid microspheres. Instead, like Mathiowitz, Lohrmann and Kayyem are limited to teachings on proteins deemed to be labile and therefore inferior by Steiner. Therefore,

Applicant submits that the combination of Lohrmann, Steiner, Kayyem and Mathiowitz would not motivate one of skill in the art to modify the teachings therein to find the present invention.

Moreover, one of skill in the art would not have a reasonable expectation of successfully producing Applicant's invention from the teachings of the cited references for several reasons. First, Mathiowitz explicitly states that any such crosslinking should not be done *during* microsphere formation (see, e.g., Mathiowitz, claim 1). And, second, Mathiowitz provides no teaching that crosslinking of amino acids during thermal condensation can successfully produce a microsphere.

Therefore, Applicant submits that the combination of Lohrmann (U.S. Patent 6,193,953), Steiner (U.S. Patent No. 4,925,673), Kayyem et al. (U.S. Patent 6, 232, 295) and Mathiowitz (U.S. Patent 5,271,961) does not produce the claimed invention and requests withdrawal of this rejection under 35 U.S.C. § 103(a) of claims 3, 4, 10 and 11.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance, and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney at (516) 795-6820 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date of Deposit: November 8, 2006
This paper or fee is being filed on the date indicated above using the USPTO's electronic filing system EFS-Web, and is addressed to: The Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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